PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant(s):	Hein et al.	
Filed:	January 9, 1998	
Art Unit:	1647	
Examiner:	David S. Romeo	
Title:	NOVEL EPITHELIAL TISSUE TARGETING AGENT	

Docket No.: 040989/283662
Customer No.: 00826

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RULE 37 C.F.R. §1.132 DECLARATION
of DR. KENDRA WHITE

I, Dr. Kendra White, do hereby declare and say as follows:

1. I am skilled in the art of the field of the invention. As set forth in my *curriculum vitae*, submitted concurrently herewith, I received a Ph.D. in Microbiology and Immunology at The University of Oklahoma Health Sciences Center, Oklahoma City, OK and obtained postdoctoral training in Molecular Immunology at The University of Texas Southwestern Medical Center, Dallas, TX and The Oklahoma Medical Research Foundation, Oklahoma City, OK. The focus of my postdoctoral training and professional work was the study of the structure/function of human IgA and mucosal immunology. I am currently employed as a Consultant for ongoing research in this field under a contract with The Oklahoma Medical Research Foundation.

2. I have read and understood the Office Actions in the above case dated July 12, 2006 and March 24, 2003.

3. The Examiner alleges in the Office Action of July 12, 2006 (page 4) that "The evidence cited by the examiner shows that although the presence of the J chain in IgA or IgM polymers is needed in order to obtain SC binding, the J chain by itself does not constitute an SC binding site." The evidence to which the Examiner refers is exemplified in the Office Action of March 24, 2003 (pages 5-8) with respect to the Examiner's discussion of Brandtzaeg *et al* (1977) *Ciba Found. Symp.*, 46:77-113. The data presented and discussed in this early publication do not determine if J chain does or does not constitute an SC binding site, only that J chain is necessary for the binding of polymeric Igs to SC. The authors state on page 85 that "We have thus demonstrated that the J chain is mandatory for a spontaneous association of SC with IgA and IgM, but the mechanism or its function in this binding process is still unknown." In the subsequent discussion, two possibilities for the role of J chain in the binding of SC to IgA/IgM polymers are addressed: 1) that J chain is indirectly necessary for binding to SC by influencing the conformation of polymeric Igs or 2) there is a direct interaction between SC and J chain. They further discuss experimental evidence that supports both possibilities. Their evidence for a direct role for J chain in SC binding is that antibodies to J chain inhibit binding of SC to Ig polymers. However, their evidence against a direct role for J chain involved flawed experimentation due to inadequate manipulation and denaturation of the J chain to counter natural aggregation and to ensure that free J chain is in fact available to bind SC. Finally, the data discussed with J chain deficient IgA/IgM does not distinguish between the two possibilities.

More recent studies published in this field support a third possibility not discussed in the early Brandtzaeg paper: that J chain plays both a direct and indirect role in the binding of polymeric Igs to pIgR. In fact, the Brandtzaeg group has subsequently published two reports that verify a direct interaction of J chain with pIgR (or SC). In a 1998 report, they showed that antibodies as well as much smaller antibody fragments against J chain inhibited the binding and transport of polymeric Igs by pIgR both *in vitro* and *in vivo* (Vaerman *et al* (1998) *Eur. J. Immunol.* 28:171-182, a copy of which is submitted concurrently herewith). In 2001, the Brandtzaeg group analyzed mutated J chains expressed with IgA and found that the C-terminus and two of the three intrachain disulfide bonds of J chain were required for transport by pIgR but not for polymerization of IgA, a copy of which is submitted concurrently herewith). Furthermore, we have published reports that support both a direct and indirect role for J chain in the interaction. In a 1999 publication, we identified a region in the Cα3 domain of dIgA that

was important for binding to pIgR and show that J chain is required for optimal binding (Hexham *et al* (1999) *J. Exp. Med.* 189:747-752, a copy of which is submitted concurrently herewith). In a subsequent report, we confirm that the Cα3 region is also important for transport and also find evidence that J chain is directly involved (White and Capra (2002) *J. Exp. Med.* 196:551, a copy of which is submitted concurrently herewith). In addition, unpublished work from our laboratory now documents the direct interaction of J chain with SC. Items 4 to 6 below present data relating to investigations of Cα3 vs. J chain interaction with SC and demonstrate that the J chain does bind SC.

4. In the 2002 publication, we used the *in vitro* MDCK transcytosis system as a means to select phage peptides that were transported by pIgR. As reported, three of the eight phage peptides that were selected by transcytosis mapped to the Cα3 region of IgA that we had previously shown to be important for binding to pIgR and were subsequently shown to direct transcytosis by pIgR. However, in unpublished results, five of the eight selected phage peptides showed considerable homology to human J chain and these alignments are shown below. The transcytosis-selected 40-mer peptides were aligned to the sequence of human J chain using the computer program LALIGN. Phage peptides are referred to by the first three amino acids of their sequences. The symbol : = amino acid identity and the symbol . = similarity.

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     40         50                    60
J    IIVPLNNRENISD      J    PTSPLRTRFVYHLSDLC
     ..:::..   .. :           : : : .. .  ::.::
SAM  MFVPFDIAVGVRD       VDD  PPSQLNSQHLL-LSQLC

       50                   110        120
J    RENIS              J    YTAVVPLVYGGE
     :: ::                   :  ::   :::.
SAM  REAIS              WQA  YLFVVATGYGGK

       10                     10
J    IVLVDNKC           J    VLVDNKCKC
     .::: :.:                : :: : .:
IPS  LVLVINRC           MFV  VCVDAK-QC
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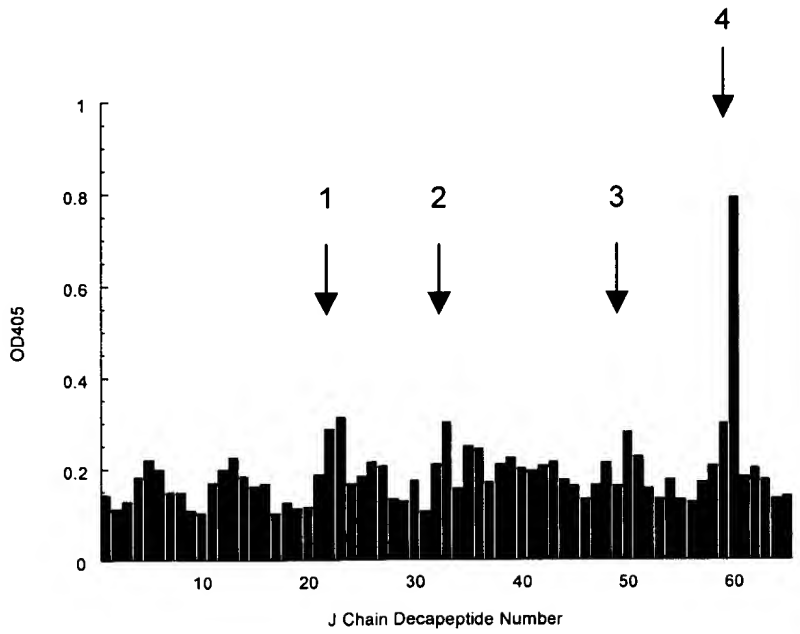
5. As shown in Item 4, when compared to portions of human J chain, the SAM peptide shares 23.1% identity in a 13 amino acid overlap and 80.0% in a 5 amino acid overlap, IPS has 62.5% identity in an 8 amino acid overlap, VDD has 41.2% in a 17 amino acid overlap,

WQA has 50.0% in an overlap of 12 amino acids, and MFV shows 55.6% identity in a 9 amino acid overlap. Identity values for the peptides compared to the negative control albumin do not show significant homology; they do not exceed 20.0% in an average of 18 amino acid overlap. We discovered that four of these five peptides were specifically transcytosed by the pIgR.

6. In unpublished data, the sequence of J chain was synthesized as decapeptides, overlapping by eight amino acids, on pins. When the J chain decapeptides were screened for reactivity with human SC, four potential binding regions in J chain were identified: 1) peptide numbers 22-23 (amino acids 42-53 in J chain), 2) 33 (amino acids 74-83), 3) 50-51 (amino acids 108-119), and 4) 59-60 (amino acids 125-136) (shown below). The interaction of the decapeptides with human SC was detected with sheep anti-SC and donkey anti-sheep IgG alkaline phosphatase. Potential reactive sites are numbered 1-4. Two of these regions were unique and two were contained within the regions of J chain previously identified by phage display for interaction with pIgR as described in Items 4 and 5. When combined, the phage and pin data identified six potential SC-binding regions in human J chain. Three of these regions are highly conserved in all species of J chain sequenced. We have produced J chain mutants based on these three conserved J chain regions and are assessing the ability of the J chain mutants to form IgA polymers, bind pIgR/SC, and be transported by the receptor. Collectively, this data demonstrates that the J chain does bind SC.



7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Kendra White, PhD

8/18/06

Dr. Kendra White
Consultant
11411 S. 69th East Ave.
Bixby, OK 74008

Date

Kendra Denise White, Ph.D.
11411 S. 69th East Ave.
Bixby, OK 74008
(918) 298-1107
Kendra-White@omrf.ouhsc.edu

EDUCATION:

University of Oklahoma, Norman, OK	B.S.	1987	Microbiology
University of Oklahoma Health Sci. Ctr., Okla. City, OK	M.S.	1990	Microbiology & Immunology
University of Oklahoma Health Sci. Ctr., Okla. City, OK	Ph.D.	1996	Microbiology & Immunology

POSITIONS AND EMPLOYMENT:

1987-1988	Microbiologist, Oklahoma State Department of Health, Oklahoma City, OK
1988-1996	Graduate student with Dr. Frank Waxman, University of Oklahoma Health Sciences Center, Department of Microbiology and Immunology, Oklahoma City, OK
1997-2001	Postdoctoral Fellow with Dr. J. Donald Capra, University of Texas Southwestern Medical Center, Dallas, TX and Oklahoma Medical Research Foundation, Oklahoma City, OK
2002-2005	Research Assistant Member, Oklahoma Medical Research Foundation, Oklahoma City, OK
2005-	Consultant

INSTITUTIONAL:

Supervisor, DNA Sequencing Core Facility, Oklahoma Medical Research Foundation, 1997-2005
University of Oklahoma Health Sciences Center, Institutional Biosafety Committee, 1999-2002

SOCIETY MEMBERSHIPS:

American Association of Immunologists
Society for Mucosal Immunology

HONORS AND AWARDS:

Alpha Epsilon Lambda
Phi Kappa Phi

1987	Harrison L. Chance Scholarship in Microbiology, University of Oklahoma
1989-1993	Provost Fellowship, University of Oklahoma Health Sciences Center
1997-1998	Leukemia Research Foundation Fellow, Oklahoma Medical Research Foundation
1999	10th International Congress of Mucosal Immunology Travel Award

PEER-REVIEWED PUBLICATIONS:

White, K.D., Frank, M.B., Foundling, S. and Waxman, F.J. (1996) *Effect of Immunoglobulin Variable Regions on C3b and C4b Deposition.* Mol. Immunol. 33:759-768.

White, K.D., Cummings, R.D. and Waxman, F.J. (1997) *Immunoglobulin N-linked Glycan Orientation Can Influence Interactions with the Complement System.* J. Immunol. 158:426-435.

Hexham, J.M., **White, K.D.**, Carayannopolous, L.N., Mandecki, W., Bristette, R., Yang, Y.S., Capra, J.D. (1999) *A Human IgA Cβ3 Domain Motif Directs Polymeric Immunoglobulin Receptor-Mediated Secretion.* J. Exp. Med. 189:747-752.

White, K.D. and Capra, J.D. (2002) *Targeting Mucosal Sites by Polymeric Immunoglobulin Receptor-Directed Peptides.* J. Exp. Med. 196:551-555.

Fukushima, N., Nalbandian, G., Van De Water, J., **White, K.**, Ansari, A.A., Leung, P., Kenny, T., Kamita, S.G., Hammock, B.D., Coppel, R.L., Stevenson, F., Ishibashi, H., Gershwin, M.E. (2002) *Characterization of Recombinant Monoclonal IgA Anti-PDC-E2 Autoantibodies Derived from Patients with PBC.* Hepatology. 36(6):1383-1392.

SELECTED ABSTRACTS:

White, K.D., Frank, M.B., and Waxman, F.J. (1993) *Structural Analysis of Immunoglobulins in Relation to Complement Activation.* XI Texas Immunology Conference, Galveston, TX.

White, K.D., Frank, M.B., and Waxman, F.J. (1994) *Structural Analysis of Antibodies in Relation to Complement Activation.* Missouri Valley Branch ASM Annual Meeting, Stillwater, OK.

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White, K.D., Hexham, J.M., Carayannopoulos, L.N., Mandecki, W., Brisette, R., Yang, Y.S. and Capra, J.D. (1999) *Binding of Dimeric IgA to the Polymeric Immunoglobulin Receptor is Directed by a Loop in the Cγ3 Domain.* 10th International Congress of Mucosal Immunology, Amsterdam, The Netherlands.

White, K.D., Girdhar, D., and Capra, J.D. (2000) *Peptide-Mediated Transcytosis via the Polymeric Immunoglobulin Receptor.* In Abstracts of AAI/CIS Immunology 2000, p. A1200, Seattle, WA.

White, K.D and Capra, J.D. (2002) *Targeting Mucosal Sites by Polymeric Immunoglobulin Receptor-Directed Peptides.* Human Antibodies and Hybridomas 2002. Bern, Switzerland.

White, K.D and Capra, J.D. (2003) *Mucosal Sites Can Be Targeted by Peptides to the Polymeric Immunoglobulin Receptor.* In Abstracts of The FASEB Journal, Immunology 2003, p. C324, Denver, CO.